REMARKS

In paragraph 3, on page 2 of the Office Action, the Examiner maintains the rejection of Claims 9-10 under 35 U.S.C. §112, first paragraph, as containing new matter.

Specifically, the Examiner contends that the specification, at page 28, only supports engraftment "up to 13 weeks", and not "for more than 13 weeks", as claimed.

Furthermore, the Examiner contends that Figure 2 is a very specific example limited to mice, wherein Balb/c mice were used as the donor and B6 mice were used as the recipient. The Examiner contends that this specific example does not provide support for a general 100% engraftment for any organ in any recipient.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

The minimum "13 weeks" in the expression "more than 13 weeks is supported at page 28, lines 10-16 of the Substitute Specification filed November 16, 2001.

Further support for 100% engraftment "more than" 13 weeks can be found in Figure 2 of the present application which shows 100% engraftment is achieved for at least 21 weeks in Group I (6.5 Gy), and for at least 36 weeks for Group II (7.0 Gy), both of which represent the present invention.

Applicants respectfully submit that the mouse model in Example 4 is a well-recognized model for humans, and thus, Example 4 reasonably conveys to one skilled in the art "any organ transplantation recipient".

It is well-known that the most difficult tissue/organ (which is susceptible to rejection) includes the skin, since major histocompatible complex (MHC) class II molecules are

highly expressed in this tissue; cytotoxic T-lymphocytes can easily recognize these molecules and kill the target cells. Therefore, if a new strategy is to be proved useful for skin transplantation, it is generally accepted that this strategy could be applicable to all organ/tissue transplantation.

Accordingly, the claims do not contain new matter, and thus Applicants request withdrawal of the Examiner's rejection.

In paragraph 7, on page 8 of the Office Action, the Examiner newly rejects Claims 9-10 under 35 U.S.C. § 112, first paragraph as containing new matter in view of the expression "wherein said graft donor is a different animal of the same species of said recipient".

Specifically, the Examiner notes that Applicants argue that support for this expression can be found in Example 4 of the specification. However, it appears that it is the Examiner's position that Example 4 is limited to mice, and thus does not support "any organ transplantation recipient".

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Again, Applicants respectfully submit that the mouse model in Example 4 is a well-recognized model for humans, and thus, Example 4 reasonably conveys to one skilled in the art "any organ transplantation recipient".

Moreover, attached hereto is a Declaration from Susumu Ikehara,[1/] one of the co-inventors of the present application, demonstrating that the present invention can

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[1/] As this Declaration is being filed in response to a rejection first raised in the outstanding Office Action, the Declaration should be considered and entered.

apply to tissue/organ allografts other than the skin of a mouse (e.g., renal or pancreas glands), and is applicable to humans. As taught in the Declaration, it is well-known that the most difficult tissues/organs (which are susceptible to rejection) are the skin and pancreas (pancreatic islets), since major histocompatible complex (MHC) class II molecules are highly expressed in these tissues; cytotoxic T-lymphocytes can easily recognize these molecules and kill the target cells. Therefore, if a new strategy is to be proved useful for skin and islet transplantation, it is generally accepted that this strategy could be applicable to all organ/tissue transplantation.

Further, recent methodologies for bone marrow transplantation (BMT) and/or organ transplantation have been established, based on experimental data mainly using mice, since it is very difficult to use non-human primates such as monkeys in transplantation research. Applicants have shown that their strategy is applicable to mice. Based on these findings, Applicants' strategy would also be applicable to humans.

Accordingly, the claims do not contain new matter, and thus Applicants request withdrawal of the Examiner's rejection.

In paragraph 5, on page 3 of the Office Action, the Examiner maintains the rejection of Claims 9-10 under 35 U.S.C. §103 as being unpatentable over Slavin et al in view of Ildstad et al, Zhang et al and Sachs et al for the reasons of record.

For the following reason, Applicants respectfully traverse the Examiner's rejection.

Specifically, the Examiner contends on page 4, second paragraph, of the Office Action, that "Applicant is respectfully reminded that the rejection is under 35 USC 103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. ...This applicant has not done, but rather argues the references individually and not their combination."

Applicants respectfully submit that the Examiner has repeatedly overlooked Applicants' arguments that there is no motivation to combine the teachings of the cited references. Applicants have thus not argued the references individually, as contended by the Examiner.

More specifically, among the cited references, only Slavin et al discloses both total lymphoid irradiation (TLI) and total body irradiation (TBI). That is to say, only Slavin et al compares TLI and TBI. However, Slavin et al teaches that TLI is preferred to TBI (see column 8, lines 63-65).

Furthermore, Tables 1-3 and EXAMPLE 2 of Slavin et al relate to skin grafts. Tables 2 and 3 of Slavin et al show the results of skin grafts performed using an immunosuppressant Cy together with sTLI of 6 fractions of 200 cGy/day, rather than 17 fractions, based on the results of Table 1. This is true even though 100% skin graft is only achieved by TLI using 17 fractions of 200 cGy (5/5) (see Table 1). That is to say, Slavin et al further indicates that sTLI is preferred compared to long TLI for a dosage of 17 fractions of TLI of 200 cGy.

Moreover, Figure 2 and EXAMPLE 9 of column 32, line 11 to column 34, line 50 of Slavin et al indicate that merely

adjusting the dose of irradiation does not improve both survival percentage and SKIN ACCEPTANCE percentage. In particular, Figure 2 of Slavin et al teaches that a higher level of irradiation leads to higher rate of death in recipients.

Regarding TBI, Slavin et al discloses only a low level of TBI, such as 400 cGy TBI, as shown in EXAMPLE 10 and EXAMPLE 11. The level of TBI used in Slavin et al is lower than that claimed in the present invention (i.e., at least 6.5 Gy).

It is clear that Slavin et al teaches and suggests that low level irradiation should be used, and, in particular, that sTLI and low level TBI should be used. Therefore, Slavin et al does not provide any reason to use a high level of irradiation, in particular a high level TBI. Thus, Slavin et al clearly teaches away from the present invention.

Ildstad et al teaches high level TBI. However, prior to the present invention, it was unpredictable whether or not a good graft could be achieved without the death of recipients, when high level TBI based on the combination of Ildstad et al and Slavin et al. Thus, there was no reasonable expectation of success by such a combination.

Further, Zang et al does not teach either TLI or TBI.

Sachs et al also teaches only low level TBI, similar to Slavin et al.

Thus, prior to the present invention, it was unpredictable whether or not a good graft could be achieved without the death of the recipients, based on the combined teaching of Zang et al and/or Sachs et al, Slavin et al and Ildstad et al.

Thus, there was no reason for a person skilled in the art to combine the cited references to achieve the present invention.

Furthermore, the Examiner states, on page 4, last line to page 5, first line of the Office Action, that "in Example 14 (of Slavin et al), it is explicitly stated that 100% of BM stromal graft and approximately 80% of the heart graft survived."

As admitted by the Examiner, in Example 14 of Slavin et al, only 80% of heart grafts were achieved by the method thereof. The present claims are directed to a 100% engraftment rate. Since Slavin et al teaches and suggests that low level irradiation should be used, as described above, one would predict that the death rate of recipients would be increased when higher TLI or TBI irradiation is performed in Example 14 of Slavin et al. Thus, prior to the present invention, it was unpredictable whether or not a good graft could be achieved without the death of the recipients, when the high level TBI taught in Ildstad et al is combined with the method of Slavin et al.

The Examiner further states, on page 6, lines 11-15 of the Office Action, that "Moreover, Applicant's attention is respectively drawn to column 17, lines 5-25 (of U.S. Patent No. 5,514,364). It is explicitly disclosed that allogeneic engraftment was reliably achieved in 100%. US '364 further teaches transplantation of organs to the bone marrow recipient and exemplifies skin transplantation, showing that the recipients are specifically tolerant of the donor-type skin (see, e.g., Abstract and columns 21-22)".

However, in column 17, lines 5-25 of Ildstad et al, organ transplantation was not performed. The result of organ (skin)

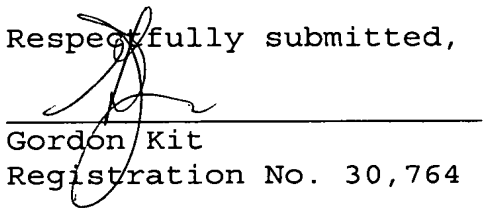
transplantation by the method of Ildstad et al is disclosed in columns 21-22 and Figure 7. The results therein show that 100% engraftment can be achieved for more than 35 days when the recipient is grafted his/her own skin (B10). However, 100% engraftment could not be achieved beyond 19 days when the recipient is grafted with donor' skin (DONOR-SPECIFIC). That is to say, Ildstad et al discloses that 100% skin engraftment can be achieved for more than 35 days when the recipient was grafted with the skin of the same animal (the same individual) of the same species as the recipient. However, 100% skin engraftment could not be achieved beyond 19 days when the recipient was grafted with the skin of a different animals (a different individual) of the same species as the recipient, as claimed in the present application.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested by Slavin et al alone or when combined with the teachings of Ildstad et al and Zhang et al, and Sachs et al and in any event, such a combination can only be made in hindsight, which is legally improper. Thus, Applicants request withdrawal of the Examiner's rejection.

In view of the amendments to the claims and arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at the telephone number listed below on any questions that might arise.

Respectfully submitted,



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Date: June 22, 2007